1-AZABICYCLIC COMPOUNDS.

22.* STEREOCHEMISTRY AND ^{13}C NMR SPECTRA OF SALTS OF PYRROLIZIDINE AND ITS HOMOLOGS WITH PROTONIC ACIDS

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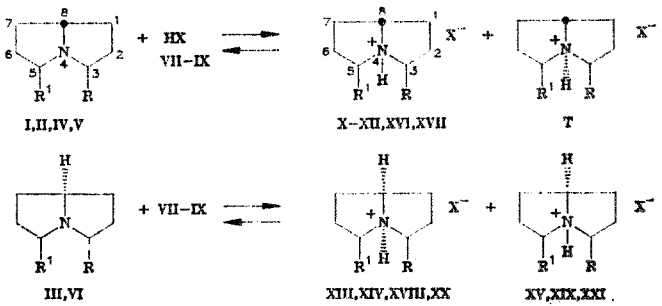
^{13}C NMR spectra were obtained for pyrrolizidinium salts and their homologs and their signals were assigned. With the exception of highly strained cis-3,8-H-cis-5,8-H-3,5-dimethylpyrrolizidine (VI), all the bases studied upon their direct mixing with CF_3CO_2H form salts only with cis-fused rings in the cation. Mixtures of salts with cis- and trans-fused pyrrolizidinium fragments are formed upon the reaction of cis-3,8-H-methyl- (III) and cis-3,8-H-cis-5,8-H-3,5-dimethylpyrrolizidine (VI) under conditions close to those for kinetically-controlled amine protonation. The ^{13}C NMR spectra of the isomeric pyrrolizidinium salts obtained as a result of the absorption of base VI by sulfuric acid were used to evaluate the conformational equilibrium in the starting compound VI. The ^{13}C NMR chemical shifts of unsubstituted trans-fused pyrrolizidinium salts were predicted.

The concepts concerning the stereochemistry of pyrrolizidinium salts and their homologs and the choice of methods to determine this stereochemistry may prove useful in examining the structure of natural and synthetic pyrrolizidinium compounds in media with high hydrogen ion concentration. We studied the salts formed upon the reaction of pyrrolizidines with acids using ^{13}C NMR spectroscopy, which has been used in previous stereochemical studies [2]. This communication is a continuation of a systematic study of the stereochemistry of pyrrolizidines [3-6].

For the reactions with acids, we selected pyrrolizidines I, II, IV and V which are virtually homogeneous relative to the type of ring fusion [5] and pyrrolizidine homologs III and IV, which are an equilibrium mixture of significant amounts of cis- and trans-fused forms [3-6]. Trifluoroacetic (VII), sulfuric (VIII) and hydrochloric acids (IX) were used.



I, X, XI R = H, II, III, V, VI, XII-XV, XVII-XXI R = CH_3, IV, XVI R = t-C_4H_9; I-IV, X-XVI R^1 = H, V, VI, XVII-XXI R^1 = CH_3, VII, X = CF_3CO_2, VIII X = HSO_4, IX, X = Cl, X, XII, XIII, XVI-XIX X^- = $CF_3CO_2^-$, XI X^- = Cl^-, XIV, XV, XX, XXI X^- = HSO_4^- (exchange of the HSO_4^- and $CF_3CO_2^-$ anions is possible for salts XIV, XV, XX and XXI in a solution of a mixture of H_2SO_4 and CF_3CO_2H).

In the general case, the formation of two types of ammonium ions differing in ring fusion is possible upon protonation of the nitrogen atoms of pyrrolizidines.

*For Communication 21, see [1].

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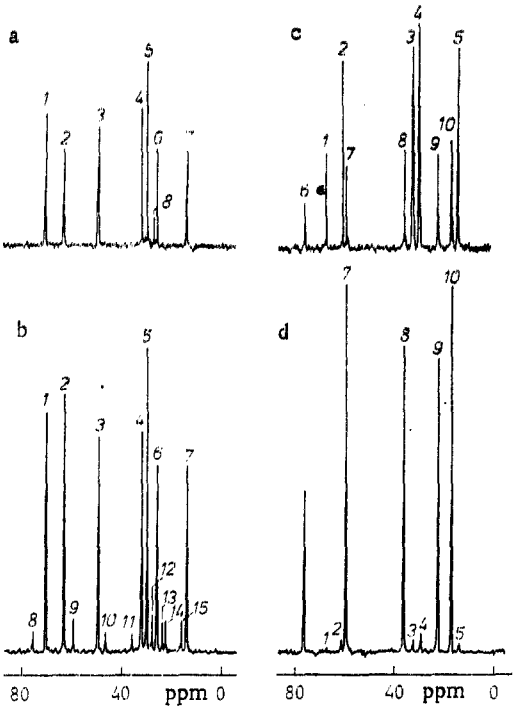


Fig. 1. ^{13}C NMR spectra of the cations of the salts obtained by the direct mixing of liquid bases III and VI with acid VII (a, c) and the absorption of the vapor of these bases by acid VIII (b, d). a: 1-7 signals of salt XIII, 8) cyclohexane signal; b: cation signals: 1-7) salts XIV, 8-15) salts XV; c: 1-5) salt XVIII, 6-10) salt XIX; d: 1-5) salt XX, 6-10) salt XXI. The assignment of the signals is given in Tables 1 and 2.

TABLE 1. ^{13}C NMR Chemical Shifts of Pyrrolizidine, Pyrrolizidine Hydrochloride and Pyrrolizidinium Trifluoroacetate*

Compound	Solvent	Concentration, mole %	$C_{(1)}, C_{(7)}$	$C_{(2)}, C_{(6)}$	$C_{(3)}, C_{(5)}$	$C_{(8)}$
I	CD_3CN	4,0	33,13	26,56	55,59	65,03
XI	CD_3CN	4,0	31,38	25,94	54,86	67,92
			(−1,75)	(−0,62)	(−0,73)	(2,89)
I	C_6H_6	6	33,25	26,81	55,72	65,08
X	CF_3CO_2H	6,9	31,29	25,33	57,17	71,14
			(−1,96)	(−1,48)	(1,45)	(6,06)

*The ^{13}C chemical shift difference $\Delta\delta$, ppm = δ(pyrrolizidinium salt) − δ (pyrrolizidine) is given in parentheses.

In the case of excess acid, the equilibrium in all cases is shifted toward the right. In addition, a high concentration of hydrogen ions prevents equilibrium interconversions of cis- and trans-fused cations (for example, salts XVIII and XIX) through deprotonation, nitrogen inversion and reprotonation. Under such conditions, the rate of proton exchange is significantly greater than the rate of nitrogen inversion [7, 8], leading to fixation of the nitrogen atom configuration even in the case of the lability of the nitrogen atom on this nitrogen atom.

The reaction of pyrrolizidines I, II, IV and V with acid VII is terminated in each case by the formation of a single salt, which is in accord with the ^{13}C NMR spectral data. The initial bases are almost entirely in cis-fused conformations and there are no data indicating the formation of type-T salts with a strained trans-fused pyrrolizidine skeleton in significant amounts.

TABLE 2. Chemical Shifts of Homologs of Pyrrolizidinium Trifluoroacetates and Bisulfates*

Compound†	Concentration, mole %	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	CH_3
XII	8,9	31,12	34,08	68,17	54,88	24,98	31,12	71,16	16,19
XIII	6,0	*30,06*	*32,43*	63,34	49,38	25,96	*30,06*	70,57	13,51
XIV	4,9	*29,76*	*32,00*	62,86	49,09	25,66	*29,76*	70,18	13,73
			(103,8)	(94,5)	(98,0)	(97,0)		(94,5)	(99,0)
XV	0,8	23,02	35,99	59,64	46,57	27,61	23,90	75,93	16,47
		(16,1)	(14,1)	(15,5)	(16,5)	(16,0)	(17,5)	(13,3)	(14,6)
XVI‡	6,5	*29,90*	*28,94*	82,80	59,35	24,96	*30,97*	73,22	26,06
XVII	4,2	30,62	33,97	66,76	66,76	33,97	30,62	71,05	17,05
XVIII	2,7	*30,92*	*33,46*	61,97	61,97	*33,46*	*30,92*	68,91	14,92
XIX	1,5	23,40	36,79	60,61	60,61	36,79	23,40	77,49	17,34
XX	0,2	*30,67*	*33,11*	61,43	61,43	*33,11*	*30,67*	68,46	14,76
		(3,45	(3,15)	(4,9)	(4,9)	(3,15)	(3,45)	(4,0)	(4,0)
XXI	6,2	23,15	36,52	59,78	59,78	36,52	23,15	76,76	17,49
		(111,8)	(107,5)	(110,0)	(110,0)	(107,5)	(118,8)	(111,5)	(211,5)

*The solutions of the trifluoroacetates in CF_3CO_2H and the solutions of the bisulfates in a 3:1 (v/v) mixture of H_2SO_4 and CF_3CO_2H. A bisulfate ⇄ trifluoroacetate equilibrium is possible in the solution of the acid mixture.
†Conditional assignment indicated by italics. The integral intensities in arbitrary units are given in parentheses. The total intensity (207.2) was found in XIV for the signals of $C_{(1)}$ and $C_{(7)}$.
‡The chemical shift of the quarternary carbon atom is 33.47 ppm.

Different behavior is observed in a study of solutions of salts prepared from bases III and VI and acids VII and VIII. In these cases, the method of salt preparation is significant. The addition of excess acid VII to pyrrolizidine III leads to the formation of one product (XIII),* while the dissolution of the vapor of this base in concentrated sulfuric acid gives a mixture of salts XIV and XV, which appears in the ^{13}C NMR spectrum as two sets of signals differing in intensity. We should note that there is not difference in the intensity distribution over time. The reaction of base VI with acids VII and VIII leads to mixtures of salts with cis- (XVII and XIX) and trans-fused pyrrolizidine systems (XX and XXI). The ratio of the isomer signal intensities in these cases is different and remains invariant over time. This finding indicates that inversion of the nitrogen atom does not occur in the time between the deprotonation of the cation and reprotonation of the free base.

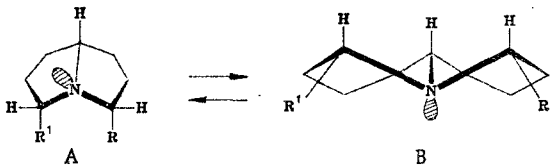
Figure 1 gives the ^{13}C NMR spectra of the pyrrolizidinium salts prepared by dissolving III and VI in acids. Spectra b, c and d show that a mixture of two salts is formed in each case. In order to confirm the isomeric nature of these salts and reject the hypothesis of the decomposition of the pyrrolizidines upon dissolution in acids, we carried out a control experiment involving neutralization of the reaction mixture obtained from pyrrolizidine homolog VI and acid VII by aqueous KOH and subsequent displacement of the free base by alkali. The ^{13}C NMR spectrum of a benzene solution of this base consisted only of five signals and was identical to the spectrum of the starting pyrrolizidine VI [4]. Thus, both compounds, whose common spectrum is shown in Fig. 1c are isomeric salts XVIII and XIX.

Comparison of spectrograms a and b and of spectrograms c and d shows that the actions of salts XIII and XIV are identical, while salts XVIII and XX have one and the same cation which is isomeric to the cation of salts XIX and XXI.

We should immediately note that the ratio of the isomeric pyrrolizidinium salts, which may be determined from the ^{13}C NMR spectra, will not reflect the conformational equilibrium of the initial base if the salts were obtained by the direct mixing of the reagents. In the

*This implies the lack of an alternative within the limits of the signal-to-noise ratio in the corresponding ^{13}C NMR spectra of the compounds studied.

case of such a procedure, complex exchange processes arise between the base and the ammonium-type ion on the boundary of the two liquid phases leading to the partial thermodynamic equilibration of the isomeric ions formed [9, 10]. Thus, the ratio of the content of salt XIX to the content of salt XVIII (0.55) cannot be given as the actual conformation equilibrium VIA $\rightleftarrows$ VIB:



A cis-fusion of the rings

B trans-fusion of the rings

Hence, the reaction of pyrrolizidine VI with concentrated sulfuric acid was carried out under conditions similar to the conditions for the kinetic control of protonation [10]. The base pairs were absorbed in a thermostatted chamber by concentrated sulfuric acid. Although the geometrical parameters of the chamber provided for a long absorption process (27 h) and the experimental conditions favored equalization of the concentrations in solution due to diffusion, a thin sulfate ring was formed on the wetting boundary of the chamber walls by sulfuric acid. The ^{13}C NMR integral intensities of salts XXI and XX indicated that the ratio of their concentrations is 34.0 ± 14.4.* According to Crowley et al. [10], the separation of a solid phase is undesirable since the ratio of the isomeric salts in this case does not completely reflect the ratio of the conformations of the initial base.

Comparison of the results for the direct mixing of acid VII and base VI and the absorption of vapor of VI by sulfuric acid shows that the fraction of the cation with trans-fusion of the pyrrolizidinium system increases upon approaching the conditions for kinetic control of the protonation of pyrrolizidine VI. Thus, for the VIA $\rightleftarrows$ VIB conformation equilibrium, the content of the VIB is greater than 95.8% and that for VIA is less than 4.2%, while $-\Delta G_{25}^{\circ} > 7.66$ kJ/mole

The assignment of the signals in the ^{13}C NMR spectra of the pyrrolizidinium salts was carried out on the basis of the ^{13}C chemical shifts (^{13}C CS) of the bases [4], comparison of the signal intensities, $^{13}C-\{^{1}H\}$ incomplete double heteronuclear resonance (DHNMR) spectra and consideration of the signal displacements due to protonation in cyclic amines [11]. For convenience of the comparison of the ^{13}C CS, their values which were initially found relative to internal standard, cyclohexane and the $^{13}CF_3$ group in CF_3CO_2H were recalculated relative to TMS by the equations $\delta_{TMS} = 27.50 + \delta_{C_6H_{12}}$ [12] for I, X-XIII, XVI-XIX and $\delta_{TMS} = 115.00 + \delta_{CF_3}$ [13] for XIV, XV, XX, and XXI.

The ^{13}C NMR spectrum of pyrrolizidinium trifluoroacetate (X) consists of four signals, of which the downfield signal at 71.14 ppm has approximately one-half of the intensity as the other three signals. Furthermore, the signal for this carbon atom in the incomplete DHNMR spectrum is a doublet due to a C—H bond. All these findings unequivocally indicate the assignment of this signal to $C_{(8)}$. In assigning the remaining signals from the three CH_2 groups, we took note of the circumstance that the displacement of the corresponding signals caused by protonation ($\Delta\delta$) in going from the free tertiary amine to a solution of the salt in CF_3CO_2H has values from -4.4 to + 4.3 ppm [11]. Even the greatest absolute displacement (4.4 ppm) [11] is not greater than the value for the least separation of the signals with CS 33.25 and 26.81 ppm (6.44 ppm) in the initial pyrrolizidine (see Table 1). Hence, the sequence of the signals for the cation of salt X is the same as in the initial base I.

The assignment of the ^{13}C CS in salts XII, XVI and XVII (Table 2) was carried out as for trifluoroacetate X taking account of the data for the latter assuming that the effects of the methyl and tert-butyl groups have the same order as in unstrained pyrrolizidines II, IV and V [4].

The reaction of partially strained base III which is conformationally heterogeneous relative to the type of ring fusion [4] with acid VII gives one of the two possible isomeric salts (Fig. 1a). Structure XIII is assigned for this salt with cis-fusion of the rings in the pyrrolizidinium cation since the ^{13}C CS of $C_{(8)}$ has a value similar to that in salts with

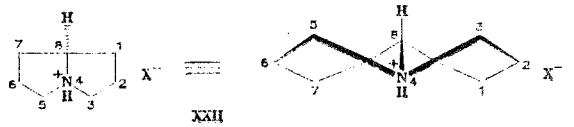
*The error margins in this work were given at the 95% confidence level.

cis ring fusion (X, XII, XVI and XVII). For final verification of the configuration of the nitrogen atom in XIII, we obtained a mixture of isomeric salts XIV and XV by dissolving vapor of base III in concentrated sulfuric acid. Salt XV differs from salt XIV by the type of ring fusion or configuration of the nitrogen atom. The signal for the methyl group carbon atom in isomer XV is located further downfield than in isomer XIV and its value (16.47 ppm) is close to a value of the ^{13}C CS of the methyl group in salt XII (16.19 ppm). Thus, the methyl group in isomer XV, in contrast to salt XIV, is free of strong nonbonding interactions, which is in accord with trans ring fusion of salt XV. The chemical shift difference of the $C_{(8)}$ atoms of isomers XIV and XV ($|\Delta\delta|$ 5.75 ppm) is relatively close to the difference in the ^{13}C CS of the same atoms ($|\Delta\delta|$ 7.1 ppm) in bases V and VI [4] and is largely a result of the difference in the nature of ring fusion, cis fusion for V and XIV and trans fusion for VI and XV. Salts XIII and XIV have the same cation and differ only in their anions. The ^{13}C NMR spectrum in Fig. 1b shows that isomer XIV which is formed in large amounts has ^{13}C CS (Table 2) similar to the corresponding shifts in salt XIII. The nature of the anion has only a slight effect on the value of the ^{13}C CS in the cation, while the role of the solvent may be more significant [14]. In the particular case considered (salts XIII and XIV), the difference in solvents (CF_3CO_2H and H_2SO_4) cannot have a significant effect on the ^{13}C CS. Thus, the cation in salt XIII, as in salt XIV, has cis ring fusion.

A pairwise examination of the ^{13}C NMR spectra of mixture is isomeric salts XVIII and XIX obtained by direct mixing of base VI and acid VII (Fig. 1c) and salts XX and XXI prepared by the absorption of the vapor of compound VI by concentrated sulfuric acid (Fig. 1d) was used to assign the groups of signals in the spectra of a specific salt differing in the type of its ring fusion (Table 2).

The identification of the signals in XIX and XXI using the chemical shift data of predominantly trans-fused base VI was carried out similarly to the assignment of the signals of salt X related to the known interpretation of the the signals in pyrrolizidine I. The assignment was supported by DHNMR data.

The determination of the assignment of the signals with ^{13}C CS 23.02, 27.61 and 23.90 ppm to $C_{(1)}$, $C_{(6)}$ and $C_{(7)}$ in salt XV requires a special approach. This assignment is made using calculation of the ^{13}C CS of B-type salts with unsubstituted trans-fused pyrrolizidinium cation XXII. The latter has an independent value since salts XXII have not yet been reported.



XXII

Since the cation of salts XXII has a plane of symmetry, four signals should be seen in the ^{13}C NMR spectrum of salts XXII. The calculation of the ^{13}C CS of the cation of salts XXII in H_2SO_4 solution was carried out by comparison of the ^{13}C CS of salts XV and XXI to determine the effects due to the 5-CH_3 group. Consideration of the effects found for the methyl group permit calculation of the ^{13}C CS in the cation of salts XXII. In this case, we considered different variants for the assignment in XV with ^{13}C CS 23.02, 23.90 and 27.61 ppm to $C_{(1)}$, $C_{(6)}$ and $C_{(7)}$. The symmetry in the ^{13}C CS for structure XXII $C_{(1)}(C_{(7)})$ 23.77, $C_{(2)}(C_{(6)})$ 27.08, $C_{(3)}(C_{(5)})$ 46.43 and $C_{(8)}$ 75.10 ppm is obtained for the following variant of the signal assignment in salt XV: $C_{(1)}$ 23.02, $C_{(6)}$ 27.61 and $C_{(7)}$ 23.90 ppm.

Thus, the procedure for calculating the ^{13}C CS in salts XXII both permits refinement of the signal assignment in the ^{13}C NMR spectrum of salt XV and obtaining the effects of methyl group at the 3(5) position of the trans-fused pyrrolizidinium cation with a hydrogen atom on nitrogen. With the exception of the γ-effect on $C_{(1)}$ ($C_{(7)}$) equal to 0.75 ppm, these effects are deshielding and have values: α = 13.21, β = -8.91, γ(on $C_{(8)}$) = -0.83, γ (on $C_{(3)}$ or $C_{(5)}$) = -0.14 ppm while the δ-effect on the methyl group at $C_{(3)}$or $C_{(5)}$ is -1.02 ppm.

The same principle for calculation of the ^{13}C CS may be used for obtaining the ^{13}C CS values in salts of the unsubstituted cis-fused pyrrolizidinium cation XXIII using the effects of the methyl groups obtained from a comparison of the ^{13}C CS of the corresponding carbons atoms in homologs X and XII, XII and XVII, XIII and XVIII, XIV and XX. In this case, we should bear in mind that the cation in salts XXIII may exist in different conformations analogous to the cis-fused conformations of free pyrrolizidine I [3].

The similarity of the methyl group effects obtained from a comparison of homologs X and XII [α = -11.00, β = -8.75, γ (on $C_{(8)}$ = -0.02, γ (on $C_{(1)}$ or $C_{(7)}$) = 0.17, γ (on $C_{(3)}$ or $C_{(5)}$) 2.29 ppm] and XII and XVII [α = -11.88, β = -8.99, γ (on $C_{(8)}$) = 0.11, γ (on $C_{(1)}$ or $C_{(7)}$) = 0.50, γ (on $C_{(3)}$ or $C_{(5)}$) 1.41 ppm) indicates a stereochemical similarity of the cations in salts XII and XVII. The calculation of the ^{13}C CS in the unsubsituted cis-fused cation of salts XXIII using the data for XII and XVII leads to the ^{13}C CS of some conformational state of the cation designated XXIIIA: $C_{(1)}(C_{(7)})$ 31.62, $C_{(2)}(C_{(6)})$ 25.09, $C_{(3)}(C_{(5)})$ 56.29 and $C_{(8)}$ 71.27 ppm. These ^{13}C NMR chemical shifts are close to those in the cation of salt X (see Table 1), which permits us to relate all three salts X, XII and XVII to the stereochemical group, in which the cations have a single conformational state.

The analogous calculation carried out for the XIII-XVIII and XIV-XX pairs leads to ^{13}C CS of $C_{(1)}(C_{(7)})$ 29.20, $C_{(2)}(C_{(6)})$ 24.93, $C_{(3)}(C_{(5)})$ 50.75 and $C_{(8)}$ 72.23 ppm for solution in CF_3CO_2H and, correspondingly, 28.85, 24.55, 50.52 and 71.90 ppm in H_2SO_4 related to a different conditional conformation state XXIIIC of cis-fused pyrrolizidinium. The distribution between the cis-fused conformations apparently differs from the conformation distribution in the cations of salts X, XII and XVII.

The signal displacements due to the effect of the positive charge upon the addition of a proton to the nitrogen atom of pyrrolizidine were found by comparison of the ^{13}C CS of the bases and trifluoroacetates in CF_3CO_2H. As later shown by Eliel and Vierhapper [14], the $\Delta\delta$ values thereby obtained (Table 1) do not have the physical significance of displacements due to protonation since the solvent is different in these two cases. Taking account of the remarks of Eliel and Vierhapper [14] relative to the work of Morishima et al. [11], we prepared pyrrolizidine hydrochloride (XI) and compared the ^{13}C CS of the corresponding atoms of the base and salt in the same solvent (CD_3CN) with the same standard (cyclohexane). Table 1 gives the ^{13}C CS of pyrrolizidine I and its hydrochloride XI as well as the corresponding displacements $\Delta\delta$. For comparision, the analogous parameters are given for the spectra of pyrrolizidine in benzene and of pyrrolizidinium trifluoroacetate (X) in CF_3CO_2H. Comparison of the $\Delta\delta$ values for the two cases given in Table 1 indicates the validity of the comments of Eliel and Vierhapper [14] on the incorrectness of using the method of Morishima et al. [14] for obtaining $\Delta\delta$ values in the case of our compounds. Nevertheless, we assume that the data of Morishima et al. [11] and of Eliel [14] on the $\Delta\delta$ values obtained by the comparison of the ^{13}C CS of base-salt pairs in different solvents may be useful as an auxiliary means in assigning the signals for the salts of other amines.

Table 1 (solutions in CD_3CH) shows that the addition of a proton to the pyrrolizidine nitrogen atom leads to shielding of the secondary carbon atoms and to a significant deshielding of the tertiary $C_{(8)}$ atom. The changes found in the ^{13}C CS due to protonation of the nitrogen atom in pyrrolizidine are similar to the effects of protonation of N-methyl-trans-decahydroquinolines [14]. The junctional carbon atom in pyrrolizidine I ($C_{(8)}$) is similar in its orientation relative to the nitrogen atom and displacement to the junctional atom $C_{(9)}$ in N-methyl-trans-decahydroquinolines [14]. The diamagnetic shift for $C_{(8)}$ in the pyrrolizidine system induced by the positive charge on the nitrogen atom ($\Delta\delta$ = 2.89 ppm) is greater than the analogous CS displacements of the junctional atom $C_{(9)}$ due to protonation of N-methyl-trans-decahydroquinolines which is 0.06 ppm for the simplest representative of this series; the maximum value of the series described by Eliel [14] $\Delta\delta$ = 2.52 ppm. We do not presently offer an explanation, for this observation and regard it as a separate finding, which upon the accumulation of suitable experimental data may prove useful for elucidating the corelations related to the $\Delta\delta$ value with the stereochemistry.

The signals for $C_{(5)}$ and the methyl groups in salt XIII are located at higher field than for salt XII. This difference is in complete accord with the structure of these isomeric salts. The cation of salt XII lacks strong nonbonding interactions, while the pyrrolizidinium ion of salt XIII has a nonbonding interaction of the C-CH_3 and 5-CH_2 groups causing mutual diamagnetic shift of the signals relative to reference compound XII by the γ-effect scheme [15]. However, this signal displacement is not the same for the carbon atoms in the 5-CH_2 and 3-CH_3 groups. While the upfield shift for the methyl group in the epimeric shift XII → XIII is 2.68 ppm, the analogous effect for $C_{(5)}$ is more than twice as great (5.50 ppm). The additional contribution to the diamagnetic shift of $C_{(5)}$ is likely a consequence of a change in the conformational equilibrium epimerization. A model for this change lies in the conditional conformational states XXIIIA and XXIIIC, in which the ^{13}C CS of $C_{(3)}(C_{(5)})$ differ significantly.

The same difference is observed in comparing the ^{13}C CS values of $C_{(3)}(C_{(5)})$ in the spectra of cis-fused isomers XVII and XVIII. The $|\Delta\delta|$ value (4.79 ppm) for this atom is the largest among the $|\Delta\delta|$ values for this isomer pair.

Thus, salts X, XII-XV, XVII, XVIII and XX may be divided into two conformational groups according to their ^{13}C NMR spectral data. The first group contains X, XII and XVII which have, with the exception of salt X, trans configuration at $C_{(3)}$(XII) and at $C_{(3)}$ and $C_{(5)}$ (XVII). The second group contains salts with cis configuration at $C_{(3)}$ or at $C_{(3)}$ and $C_{(5)}$, namely, XIII, XIV, XVIII and XX which show signals for $C_{(3)}$ and $C_{(5)}$ at higher field than for the isomers of the first group.

The signals for the methyl groups of the salts with trans ring fusion (XIX and XXI) are at lower field than the methyl group signals of the isomeric salts with cis ring fustion (XVIII and XX) by 2.5 ppm on the average. The pronounced difference in the ^{13}C NMR spectra of these isomeric salts affects the position of the signals for their junctional $C_{(8)}$ atoms. The signals for the trans-fused salts are at lower field than for the cis-fused salts and the difference in their CS was 8.3 and 8.58 ppm, depending on the solvent. This difference is close to that for the same atoms (7.1 ppm) in isomeric bases V and VI differing in the type of ring fusion [4]. In addition, the cis- and trans-fused cations of salts XIV and XV, XVIII and XIX, and XX and XXI differ markedly in their ^{13}C CS for $C_{(1)}$ and $C_{(7)}$. In contrast to the signals for the $C_{(8)}$ atoms of these salts, the signals for $C_{(1)}$ and $C_{(7)}$ in the salts with trans-fused rings are found at higher field than for salts with cis-fused pyrrolizidine bicyclic systems. Taking account of the possible alternative assignments of the signals for $C_{(1)}$ and $C_{(2)}$ in salt XIV and of $C_{(1)}(C_{(7)})$ and $C_{(2)}(C_{(6)})$ in salts XVIII and XX, we find that the $|\Delta\delta|$ values of the atoms examined for the cis- and trans-fused isomers may be found in the range from 5.86 to 10.06 ppm.

Thus, the chemical shift of the junctional atom $C_{(8)}$ and of $C_{(1)}$ and $C_{(7)}$ in both free pyrrolizidines and pyrrolizidinium salts may serve as a fundamental criterion for determining the predominant type of ring fusion in the case of $C_{(8)}$ and for the assignment of the cation of the salt to the cis- or trans-fused series in the case of $C_{(1)}$ and $C_{(7)}$.

An examination of models of the cations of salts XIII, XIV, XVIII and XX shows that there are significant nonbonding interactions in the cation of salt XIII and XIV between the 3-CH_3 and 5-CH_2 groups and rather strong nonbonding interactions between the methyl groups in the cation of XVIII and XX. The γ-interaction of the 3-CH_3 and 5-CH_2 group, as shown above, is clearly seen in the ^{13}C NMR spectra. In contrast, the presumably strong nonbonding interactions of the methyl groups in the cation of salts XVIII and XX have ordinary effects on the chemical shifts of the methyl groups. These δ-effects were found by comparison of the ^{13}C CS of the methyl groups in the following homolog pairs:* II and V (-0.9) [4], XV and XXI (-1.02), XIV and XX (-1.03), XIII and XVIII (-1.41), XII and XVII (-0.86 ppm). The $C_{sp^3}-N_{sp^3}$ bond length (1.47 Å) [16] differs only slightly from the the $C_{sp^3}-N^+_{sp^3}$ bond length (1.48 Å) [17] (although a value of 1.516 A has been reported [18]) and, thus, we may expect a strong mutual steric compression of the methyl groups in the cation of salts of salts XVIII and XX. In light of the data of Grover et al. [19] on the δ-effect of close-lying groups in carbocyclic compounds (up to 5 ppm), the value of the δ-effect of the methyl groups in salts XVIII (-1.41) and XX (-1.03 ppm) is unexpected.

We previously described the case of the formation of a quaternary pyrrolizidinium salt with a fixed trans-fused pyrrolizidinium fragment [21]. In the present study, ^{13}C NMR spectroscopy is used to provide evidence for the first case of the formation of trans-fused pyrrolizidinium cations, in which there are reversible fixation of the nitrogen configuration due to proton addition.

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EXPERIMENTAL

The ^{13}C NMR spectra of pyrrolizidine I in solution in benzene and CD_3CN and of solutions of salt XI in CD_3CN, salts X, XII, XIII, and XVI-XIX in CF_3CO_2H, and of salts XIV, XV, XX,

*The negative sign for the effect indicates that the ^{13}C signal for the first methyl group upon the action of the introduced second methyl group is shifted downfield.

and XXI in 3:1 H_2SO_4–CF_3CO_2H were taken on a Varian XL-100-15FT spectrometer at 25.16 MHz, Varian CFT-20 spectrometer at 20 MHz, and Varian FT-80A spectrometer at 20 MHz under condition of complete and incomplete ^{13}C–{^1H} spin coupling suppression by means of noise modulation using a pulse accumulation mode with subsequent Fourier transformation. The resonance conditions were stabilized relative to the deuterium nuclei in CD_3CN, C_6D_6, D_2O or CD_3OH. In the three latter cases, the solvent containing deuterium was placed in a 3-mm-diameter cyclindrical ampule which set coaxially in a standard ampule with the sample studied. The ^{13}C CS for solutions of salts in H_2SO_4–CF_3CO_2H mixtures were measured relative to the center of CF_3 group quartet. In the other cases, cyclohexane was the internal standard. The experimental ^{13}C CS were converted to values relative to TMS in the ordinary way using data for the ^{13}C CS of cyclohexane and CF_3CO_2H relative to TMS [12, 13].

Samples of pyrrolizidines I-VI were obtained according to our previous procedures [5].

Pyrrolizidinium chloride (pyrrolizidine hydrochloride) (XI) was obtained by passing a stream of dry hydrogen chloride into a solution of pyrrolizidine in dry ether. The precipitate of XI was filtered off and recrystallized twice from 2-butanone. In light of high hygroscopicity, all the operations for the isolation and purification of these compound were carried out in dry argon. The melting point (222.5-226.5°C) was determined in sealed capillaries filled with argon. Found: C, 56.7; H, 9.4; N, 10.4%. Calculated for $C_7H_{13}N \cdot HCl$: C, 56.9; H, 9.6; N, 9.5%.

Solutions of pyrrolizidinium (X), trans-3,8-H-3-methyl-cis-4,8-H- (XII), cis-3,8-H-3 methyl-cis-4,8-H- (XIII), trans-3,8-H-3-tert-butyl-cis-4,8- (XVI), trans-3,8-H-cis-4,8-H-trans-5,8-H-3,5-dimethyl- (XVII), mixture of cis-3,8-H-cis-4,8-H-cis-5,8-H-3,5-dimethyl- (XVIII) and cis-3,8-H-trans-4,8-H-cis-5,8-H-3,5-dimethylpyrrolizidinium trifluoroacetates (XIX) in trifluoroacetic acid were prepared as follows. Bases I-VI (0.2-0.3 g) were introduced into NMR tubes and then 1.4-2.5 ml trifluoroacetic acid was added gradually with stirring of the tube contents and water cooling.

Soultions of cis-3,8-H-3-methyl-cis-4,8-H- (XIV) and cis-3,8-H-3-methyl-trans-4,8-H-pyrrolizidinium bisulfates (XV) and a mixture of cis-3,8-H-cis-4,8-H-cis-5,8-H-3,5-dimethyl- (XX) and cis-3,8-H-trans-4,8-H-cis-5,8-H-3,5-dimethylpyrrolizidinium bisulfates (XXI) in sulfuric acid were obtained by the absorption of the vapors of these bases by conc. sulfuric acid. The reaction was carried out in a 53-ml thermostatted cyclindrical glass chamber with 3.5 cm base diameter. A cup with approximately 1 cm^2 base are was suspended from the ground stopper of the chamber. A sample of 1.5 ml conc. H_2SO_4 was poured onto the bottom of the chamber and 0.3 g base III or VI was added to the cup. The chamber was closed by stopper and maintained at 25°C until there was no amine in the cup. This process required 52 h for the binding of base III and 27 h for base VI. A thin white salt ring was formed on the wetting boundary of the chamber walls by sulfuric acid. A sample of 0.5 ml CF_3CO_2H was added to the salt solutions obtained in sulfuric acid in order to reduce their viscocity. Trifluoroacetic acid also served as as the internal standard in the ^{13}C NMR spectra.

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STERIC CONTROL OF THE ASYMMETRIC SYNTHESIS OF N-SUBSTITUED 2-METHYL-4-PIPERIDONES

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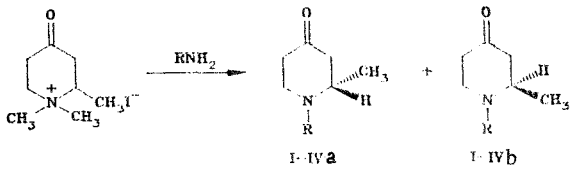
Transmission of the iodomethylate of 1,2-dimethyl-4-piperidone by (S)-sec-butylamine gives 1-(S-sec-butyl)-2S-methyl-4-piperidone in 33% optical yield while transamination by (S)-1-methyl-2-phenylethylamine gives a 1:1 diastereomeric mixture of 1-(1-methyl-2-phenylethyl)-2-methyl-4-piperidone. The decrease in the optical yield is related to the facile opening of the piperidone ring at the C–N bond with subsequent recyclization. The ^{13}C NMR data indicate that all the diastereomers of the 4-piperidones obtained are in the chair conformation with predominantly equatorial orientation of the methyl group at $C_{(2)}$. The chiral optical properties were studied and the absolution configurations of the 4-piperidones obtained were established.

We studied the reaction of the iodomethylate of 1,2-dimethyl-4-piperidone with (S)-(+)-sec-butylamine and (S)-(+)-1-methyl-2-phenylethylamine in order to determine the sterochemical features of this asymmetrical synthesis and expand the series of chiral 4-piperidones [1] which are synthones for the preparation of many biologically active compounds. The action of equimolar amounts of 1,2-dimethyl-4-piperidone iddomethylate with 1-methyl-2-phenylethylamine in the presence of excess water at room temperature gives a 48% yield of 1-(1-methyl-2-phenylethyl)-2-methyl-4-piperidone (I), which was shown to be a 1:1 mixture of isomers Ia and Ib by thin-layer chromatography on Silufol plates and gas liquid chromatography on a glass capillary column.



I R = $CH(CH_3)CH_2C_6H_5$; II R = $CD(CD_3)CD_2C_6H_5$; III R = $CH(CH_3)C_2H_5$; IV R = $CH(CH_3)C_6H_5$

In the light of the very slight difference in the chromatographic mobility ($\Delta R_f < 0.1$) isomers Ia and Ib could be separated only using preparative chromatography on Silufol plates.

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